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(54) Title: ALCOHOL-ESTER SEPARATION BY REACTION WITH BICARBONATE IN POLYHYDROXY SOLVENT

(57) Abstract

A process is disclosed for the isolation of an enantiomerically enriched ester from a first mixture of an enantiomerically enriched alcohol and an enantiomerically enriched ester, said process comprising the steps of: (a) contacting said mixture with a reagent capable of reacting with the alcohol function of said alcohol to produce a second mixture containing enantiomerically enriched unreacted ester and a compound more volatile than said ester; said reagent comprising a metal bicarbonate and a polyhydroxy solvent containing from 2 to 4 carbon atoms; and (b) removing the volatile compound from the second mixture, leaving behind enantiomerically enriched ester. The enantiomerically enriched ester can be used directly or can be converted to an enantiomerically enriched alcohol.

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ALCOHOL-ESTER SEPARATION BY REACTION WITH BICARBONATE IN POLYHYDROXY SOLVENT

Industrial Field

The present invention relates to a process for producing enantiomerically enriched compounds from a mixture which can be derived from the enzymatic enantioselective hydrolysis of a racemic ester or the enzymatic enantioselective esterification of a racemic alcohol. The resulting enantiomerically enriched compounds find a number of uses as starting materials for other compounds. Some of the compounds are useful, for example, for the production of 2-deoxy-D-ribose. Other compounds are useful in the preparation of leukotrienes.

Background Art

Chemoenzymatic synthesis is a preparative strategy which employs both chemical and biocatalytic steps in a reaction sequence. The biocatalytic transformations convert one organic compound to another by the use of enzymes, either isolated or as part of biological systems. These biocatalysts (enzymes) are in principle the same as any other type of catalyst. However, there are circumstances where these biocatalysts are especially useful, such as the induction of chirality due to enzyme enantiospecificity. These enzymatic reactions occur under mild conditions and are often more environmentally acceptable than classical chemical processes.

Lipases are the closest to optimum biocatalysts. They are isolated extracellular enzymes whose natural function is to hydrolyze glycerol esters. Many have wide substrate acceptability for ester hydrolysis, or, under the correct conditions, alcohol esterification. They are readily (and often cheaply) available and are

experimentally simple, requiring no added cofactors and affording no side products. Not surprisingly these enzymes have been the most thoroughly studied for biocatalytic use in organic chemistry.

There are two types of substrate classes for lipase-catalyzed reactions. Meso or prochiral substrates constitute the first and most widely-studied class. The inherent chirality of the lipase distinguishes between two prochiral functions (esters or alcohols) on the same molecule to afford 100% conversion to (optimally) a single enantiomer.

The second class of substrates are the racemic systems, in which (optimally) only one of two enantiomers is recognized and hydrolyzed (or esterified) by the lipase, affording a 50% conversion to product and 50% recovered starting material of opposite configurations. This mixture must be physically separated to complete the enantiomeric differentiation. For substrates in which the acid rather than the alcohol portion is of interest, the separation is often possible by simple aqueous base extraction.

Alcohol-based substrates pose the most challenging separation problems due to the gross physical similarity between the alcohol and ester. It is to separations of this type that the present invention is directed.

Chemoenzymatic synthesis of optically active epoxybutadiene (hereinafter EpB) is a potentially attractive preparative method since a readily available source of EpB has recently become available. Novel, simple, and efficient preparations of optically pure C4 synthons derived from EpB would be synthetically useful, since most currently available chiral synthons have a three- or five-carbon backbone

due to availability from natural sources. In fact, chain elongation of C3 synthons from the chiral pool currently comprises the major method for the preparation of optically active EpB and the corresponding diol (1,2-dihydroxy-3-butene).

For example, an early route to *S*-1,2-dihydroxy-3-butene and *S*-EpB relied on C6 D-mannitol (two identical three-carbon pieces) as the chiral starting material. (Baer, E.; Fischer, H. O. L. J. Biol. Chem. 1939, 128, 463) After formation of the terminal (symmetrical) diacetonide, the vicinal diol was oxidatively cleaved with lead tetraacetate to provide two molecules of the unstable acetonide of the three-carbon synthon *R*-glyceraldehyde. Wittig reaction with methylene triphenylphosphorane afforded 1,2-dihydroxybutene acetonide which was readily deprotected to the optically active 1,2-dihydroxybutene. Monotosylation of the diol and base treatment afforded optically active EpB. (Crawford, R. J.; Lutener, S. B.; Cockcroft, R. D. Can. J. Chem. 1976, 54, 3364.)

The corresponding *R* enantiomers were available from the antipodal three carbon synthon *S*-glyceraldehyde acetonide which has been prepared from L-ascorbic acid by several routes. After initial differential protection of the hydroxyl groups by sequential actonide formation and methylation, ozonolysis and lithium aluminum hydride treatment afforded *S,S*-1,2,3,4-tetrahydroxybutane 1,2-acetonide. Lead tetraacetate oxidative cleavage resulted in the desired *S*-glyceraldehyde acetonide. This material can be transformed to optically active *R*-1,2-dihydroxy-3-butene and ultimately to *R*-EpB.

Alternatively, optically active 1,2-dihydroxy-3-butene can be prepared from one of the few four carbon

synthons available from the chiral pool, tartaric acid. After preparation of the acetonide and reduction of the carboxyl groups, formic acid-induced rearrangement and hydrolysis of the resulting formates afforded the desired diol. This can be transformed to optically active EpB.

All routes suffer from synthetic problems. The oxidation steps mentioned above can be troublesome and produce highly toxic (lead) by-products. The first two routes also involve a cumbersome Wittig olefination of glyceraldehyde acetonide, itself a rather unstable species. In addition, each of the two routes can only be utilized for a single (but complementary) enantiomer due to the commercial availability of only D-mannitol and L-ascorbic acid. The route from tartaric acid is complicated by the formation of 1,4-dihydroxy-2-butene during the rearrangement reaction. Separation of this isomer from the desired 1,2-dihydroxy-3-butene is not trivial.

In actuality, only the route from tartaric acid is directed towards C4 synthons. The other schemes afford C4 materials as an afterthought by chain extension. A more direct approach, the synthesis of optically active C4 synthons from corresponding racemic C4 starting materials, would afford greater versatility for the preparation of diverse organic molecules. Therefore, the preparation of optically active EpB and derivatives (from racemic EpB) using biocatalysis technology is of great interest. An enantioselective lipase-catalyzed hydrolytic approach to this problem seemed promising due to the presence of diverse oxygen functionalities in many EpB derivatives.

EpB can be converted to a racemic ester by a number of routes. This ester is then subjected to

enzymatic enantioselective hydrolysis to produce a mixture of enantiomerically enriched alcohol and enantiomerically enriched ester. While these compounds can be separated using chromatographic separation techniques, this is not practical on a large scale. Unfortunately, as mentioned previously, the separation of the alcohol from the ester is difficult because of the similarity of the physical characteristics of these compounds.

Thus, the present invention is directed to the problem of separating an optically active ester from a mixture of the ester and the alcohol.

Disclosure of the Invention

In accordance with the present invention, there is provided a process for the isolation of an enantiomerically enriched ester from a first mixture of an enantiomerically enriched alcohol and an enantiomerically enriched ester, said process comprising the steps of:

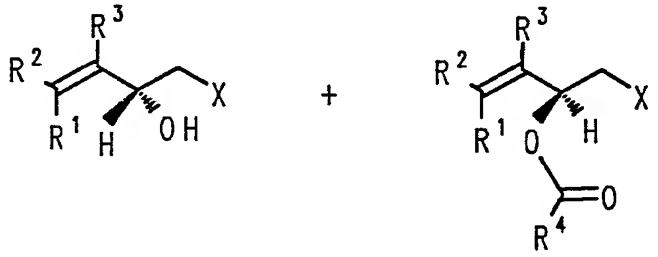
(a) contacting said mixture with a reagent capable of reacting with said alcohol to produce a second mixture containing enantiomerically enriched unreacted ester and a compound more volatile than said ester; said reagent comprising a metal bicarbonate and a polyhydroxy solvent containing from 2 to 4 carbon atoms; and

(b) removing the volatile compound from the second mixture, leaving behind enantiomerically enriched ester. The enantiomerically enriched ester can be used directly or can be converted to an enantiomerically enriched alcohol by hydrolysis.

The invention is particularly useful in separating the alcohol and ester that are formed by the enzymatic enantioselective hydrolysis of a racemic acetate or enzymatic enantioselective esterification

of a racemic alcohol, either of which is in turn formed from 3,4-epoxy-1-butene (EpB). Thus, the invention is particularly useful for the isolation of an enantiomerically enriched 1-arylsulfonate-2-acyloxy-3-butene from a mixture containing the 1-arylsulfonate-2-acyloxy-3-butene and a 1-arylsulfonate-2-hydroxy-3-butene.

In preferred embodiments, the mixture is represented by:



wherein each R is a group stable to mildly basic conditions and is independently selected from H, straight- or branched-chain substituted or unsubstituted alkyl, aryl, substituted aryl, arylalkyl, non-nitrogen-containing heteroaryl or substituted heteroaryl, or halogen. Substituents as designated above can be chosen from halogen, alkoxy, aryloxy, cyano, arylthio, alkylthio.

X is selected from halogen (F, Cl, Br, I) or sulfonate esters such as p-toluenesulfonate, phenylsulfonate, p-bromobenzenesulfonate, 4-chloro-3-nitrobenzenesulfonate, 2,5-dichlorobenzenesulfonate, 5-dimethylamino-1-naphthalenesulfonate, 2,4-dinitrobenzenesulfonate, p-iodobenzenesulfonate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, o-nitrobenzenesulfonate, m-nitrobenzenesulfonate, p-nitrobenzenesulfonate, 2-thiophenesulfonate, methanesulfonate, trifluoromethanesulfonate, and the like.

In the first step of the process of the invention, the mixture is reacted with reagents that react with the alcohol component of the mixture so as to produce a compound that is more volatile than is the ester. The usual compound that is desired is an epoxide formed from the alcohol.

Conditions for the selective epoxide-forming reaction utilize a metal bicarbonate of the formula MHCO3, where M = Na, K, Cs, or R4N where R is as defined above. The reaction is performed in a polyhydroxy solvent containing 2 to 4 carbon atoms such as ethylene glycol, propylene glycol, 1,3-propanediol, and 1,2-, 1,3-, 1,4-, or 2,3-butanediols. The reaction can be performed at or below room temperature such that the hydroxy compound is consumed in a reasonable amount of time (<72 h). The currently preferred bicarbonate is potassium bicarbonate and the currently preferred solvent is ethylene glycol.

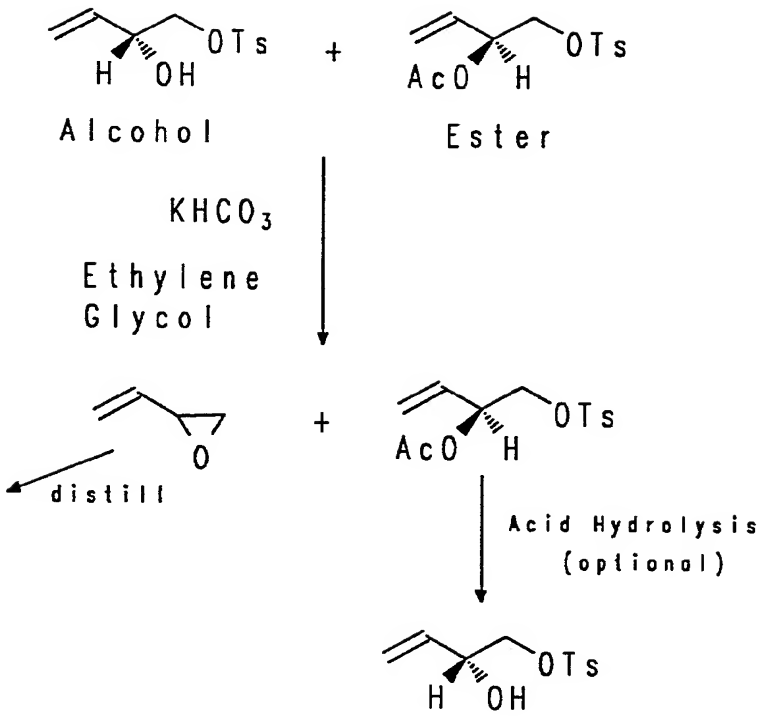
It is particularly surprising that reaction in the solvent as defined is successful since reaction in closely related solvents, e.g. monohydroxy solvents, do not give the desired results.

In the second step of the process, the volatile compound, preferrably EpB, is removed from the mixture such as by distillation.

The resulting ester can be converted to the parent alcohol by acid hydrolysis. For example, hydrochloric acid in methanol at about pH 1.0 is suitable for this reaction.

The resulting hydroxy-tosylate can be purified by recrystallization to substantial optical purity.

Thus, the process of the invention can be illustrated, in its preferred embodiment, by the following reaction scheme:



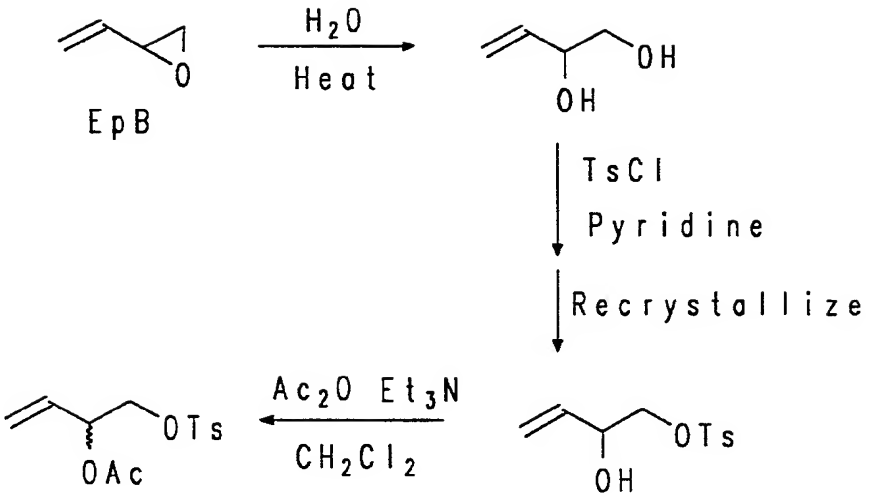
The invention relates to a method for the separation of an enantiomerically enriched ester from an enantiomerically enriched alcohol. The preparation of a typical mixture of this type will be discussed. In this process, EpB is first converted to a racemic acetate. This acetate is then subjected to enzymatic hydrolysis to produce the desired starting mixture. It will be understood, however, that the method of obtaining the desired mixture as well as the particular mixture itself or proportions thereof is not critical to the invention in its broadest aspect. The described route is merely a preferred route.

A useful racemic ester starting substrate for enzymatic hydrolysis can be prepared from EpB by two routes. For efficiency, a tosylate group was chosen as the 1-alkoxy substituent to allow ready intramolecular displacement to form the volatile compound from the alcohol. (In preferred embodiments,

this volatile compound is EpB, as is shown above.) In addition, enzymatic hydrolysis of tosylated glycerol derivatives has been reported. (Hamaguchi, S.; Ohashi, T.; Watanabe, K. Agric. Biol. Chem. 1986, 50, 1629.) Groups other than tosylate can be used when other considerations become more important.

The 1-tosyloxy-2-acetoxy-3-butene substrate is also preferred since it can be hydrolyzed with high *R*-enantioselectivity by common lipases, affording a rapid route to optically active EpB.

The racemic acetate substrate was prepared by one of two methods. The diol route began with racemic 1,2-dihydroxy-3-butene which could be prepared by reacting EpB with water under neutral conditions or with acid catalysis. The diol was treated with p-toluenesulfonyl chloride (p-TsCl) in pyridine at 4°C to afford the desired monotosylate contaminated with about 10% of the corresponding ditosylate. The monotosylate could be selectively crystallized to afford pure monotosylate in 61% yield. Hydroxy-tosylate was acetylated under normal conditions (Ac2O, Et3N, CH2Cl2) to provide the acetoxy-tosylate (the desired racemic acetate) in 93% yield. The diol route is illustrated as follows:



Racemic ester

Alternatively, the acetoxy-tosylate could be prepared by initial reaction of EpB with acetic acid under palladium(0) catalysis to afford 1-hydroxy-2-acetoxy-3-butene. Tosylation under normal conditions (p-TsCl, Et3N, CH2Cl2, 88%) afforded the desired product. However, the isomeric inconsistency of the monoacetate material (acetyl migration during distillative purification) and the inseparability of the positional isomers of two intermediates posed significant problems, since the unwanted isomers complicated the enzymatic hydrolysis. Therefore, the former (diol) preparation is preferred.

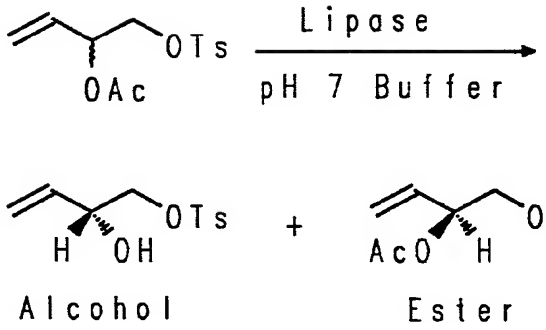
In the next step, the racemic ester was hydrolyzed in the presence of a lipase. (Convenient lipases are Lipase SAM-II® derived from Pseudomonas fluorescens and Lipase PS-30® derived from Pseudomonas cepacia, both commercially available from Amano International Enzyme Company.)

The enzymatic enantioselective hydrolysis of the racemic ester proceeds using only a small amount (e.g., 50 mg crude lipase/0.1 mol racemic ester) of the lipase from Pseudomonas fluorescens or from

Pseudomonas cepacia. The reaction can be performed as an emulsion in aqueous pH 7 phosphate buffer under automatic titration conditions ("pH Stat", end point pH 7.00), allowing the reaction to be followed by the uptake of 1.000 N NaOH. The reaction can be stopped at about 50% conversion, affording the *R*-enantiomer of the optically active alcohol and unreacted *S*-ester. The *R*-selectivity of the hydrolysis is very high, affording both enantiomers in high optical purity [both >80% enantiomeric excess (ee)] with an *R* to *S* hydrolysis rate ratio (E value) of between 200 and 300. This is what is meant by "enantiomerically enriched". (The E value is determined in accordance with the methods described in (a) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. J. Am. Chem. Soc. 1982, 104, 7294. or (b) Chen, C. S.; Wu, S. H.; Girdaukas, G.; Sih, C. J. J. Am. Chem. Soc. 1987, 109, 2812.) In the same manner, "substantially optically pure" means >98% ee.

Alternatively, the lipase isolated from Pseudomonas Novo sp. ATCC 21808 can be used, affording the same configurational selectivity with an E value of upwards of 300.

A solution or well-dispersed emulsion is important for the success of an enzymatic hydrolysis reaction. In certain instances the mixture of optically active alcohol and optically active ester formed an undesirable gel prior to completion of the hydrolysis, halting the reaction early. A 9:1 pH 7 Buffer:tetrahydrofuran solvent mixture avoided this problem and also afforded a more rapid hydrolysis reaction (rate increased by a factor of 2) without sacrificing enantioselectivity (E values of up to 254 were observed). The enzymatic hydrolysis is illustrated as follows:



Substrate Preparation and Enzymatic Hydrolysis

Diol Preparation

Addition of Water to EpB

EpB (250g) was added to 800 mL of water, followed by 10 g of an acid resin. The reaction mixture was stirred at room temperature overnight. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure. Distillation of the residue (60-65°C/1mm) provided 3,4-dihydroxy-but-1-ene in 85% yield. ^{1}H NMR (CDCl3): 5.9 (m, 1H); 5.4-5.2 (m, 2H); 4.25 (m 1H); 3.7 (m, 1H); 3.5 (m, 1H); 2.3 (br s, 1H). Ir(CCl4): 3600, 3499 (broad), 2900, 2880 cm^{-1}. Ms: 87, 70, 57, 42, 31, 29 m/e.

1-Tosyloxy-2-hydroxy-3-butene

(Racemic Ester, diol route)

1,2-Dihydroxy-3-butene (20.00 g; 0.227 mol; 1.05 equiv) was dissolved in pyridine (200 mL). The reaction mixture was cooled in an ice bath and p-toluenesulfonyl chloride (p-TsCl) (41.11 g; 0.216 mol) was added in four portions over 30 min. After thorough mixing, the reaction mixture was placed at 4°C for 18 h, at which time thin layer chromotography (hereinafter TLC) analysis indicated no p-TsCl. The mixture was concentrated to about half the original volume at reduced pressure from a 40°C water bath and

then diluted with ether (200 mL). The mixture was washed with water (100 mL), ice-cold 3 N HCl until the washes remained acidic (2x100 mL), and saturated sodium bicarbonate (100 mL). After drying the organic solution ($MgSO_4$), the solvent was removed to afford 41.73 g of a 91:9 mixture (^1H nmr analysis) of the desired compound and the corresponding di-tosylate. The crude product solidified over several days at -20°C. It was recrystallized from methylene chloride (50 mL) by the addition of hexanes (100 mL) and chilling to -20°C to afford two crops (total 33.33 g; 61%) of the desired compound which was pure by TLC analysis, mp 38-44°C. ^1H nmr (300 MHz, $CDCl_3$): 7.800 (2H, d, J=8.25 Hz); 7.356 (2H, d, J=8.19 Hz); 5.751 (1H, ddd, J=5.38, 10.46, 16.55 Hz); 5.378 (1H, br d, J=17.05 Hz); 5.247 (1H, br d, J=10.48 Hz); 4.396 (1H, m); 4.066 (1H, dd, J=3.39, 10.20 Hz); 3.906 (1H, dd, J=7.41, 10.22 Hz); 2.451 (3H, s); 2.276 (1H, d, J=4.50 Hz). IR (KBr, cm^{-1}): 3520 (s,b); 1650 (w); 1600 (s); 1350 (s); 1170 (s). Combustion Analysis: Theor - C, 54.53; H,5.82; N, 0. Found - C, 54.84; H, 5.86; N, <0.3.

1-Tosyloxy-2-acetoxy-3-butene

Tosylate from above (25.00 g; 0.103 mol) was dissolved in methylene chloride (125 mL) and cooled to 0°C. Triethylamine (21.5 mL; 0.155 mol; 1.5 equiv) was added followed dropwise by acetic anhydride (11.7 mL; 0.124 mol; 1.2 equiv). The reaction mixture was allowed to warm to room temperature and after 2.5 days no starting tosylate was visible by TLC analysis. The mixture was poured into ether (250 mL), washed with water (2x50 mL) and saturated sodium bicarbonate (50 mL), dried ($MgSO_4$), and concentrated. The crude product was stirred with pH 7 phosphate buffer (100 mL) for 1.5 h to hydrolyze any excess acetic anhydride

and extracted with ether (3x50 mL). The combined ether extracts were dried (MgSO4) and concentrated to afford 27.51 g (93%) of acetate product. ^{1}H nmr (300 MHz, CDCl3): 7.786 (2H, d,J=8.26 Hz); 7.355 (2H, d, J=8.03 Hz); 5.710 (1H, ddd, J=6.23, 10.54, 17.05 Hz); 5.396 (1H, m); 5.324 (1H, d, J=16.72 Hz); 5.279 (1H, d, J=10.63 Hz); 4.09 (2H, m); 2.453 (3H, s); 2.017 (3H, s). IR (neat film, cm^{-1}): 1740 (s); 1645 (w); 1600 (m); 1360 (s); 1175 (s).

Optically active *R*-(+)-alcohol ($[\alpha]D^{20}$ +7.14°(c. 1.036, methanol)) afforded *R*-(+)-ester, $[\alpha]D^{20}$ +5.30° (c. 1.246, methanol), by this methodology.

Enzymatic Enantioselective Hydrolysis of Racemic Ester using SAM-II

Racemic ester described above (25.76 g; 90.6 mmol) and pH 7 phosphate buffer (90 g) were combined and vigorously stirred under pH Stat conditions (automatic titration - pH 7.00 end point). Once the pH had stabilized at 7.00, the lipase from Pseudomonas fluorescens (SAM II) (50 mg) was added. The mixture was stirred for 15 h under pH Stat conditions at which time 45.54 mL of 1.000 N NaOH had been consumed. The mixture was extracted with methylene chloride (3x100 mL), dried (Na2SO4), and concentrated to afford 23.47 g (98% material recovery) of the mixture of alcohol and ester. A portion (about 350 mg) was flash chromatographed (elution with 1:2 ethyl acetate:hexanes) to afford *R*-alcohol (148 mg; 92% ee) and *S*-ester (195 mg; 94% ee). Enantiomeric excess was determined using a method analogous to that described in Dale et al, J. Org. Chem., 1969, Vol 33, p2543.

R-alcohol: $[\alpha]D^{20}$ +7.14° (c. 1.036, methanol)

S-ester: $[\alpha]D^{20}$ -5.29° (c. 1.324, methanol).

All other properties are as described above for the alcohol and the ester.

Enzymatic Enantioselective Hydrolysis of Racemic Ester using the lipase from Pseudomonas Novo Sp. ATCC 21808

Racemic ester prepared as above (1.42 g; 5.00 mmol) and pH 7 phosphate buffer (20 g) were combined and vigorously stirred under pH Stat (automatic titration - pH 7.00 end point) conditions. Once the pH had stabilized at 7.00, an ammonium sulfate suspension of the lipase from Pseudomonas novo Sp. ATCC 21808 (1.00 mL) was added. The mixture was stirred for 4 h under pH Stat conditions at which time 2.471 mL of 1.000 N NaOH had been consumed (49.4 % conversion). The mixture was extracted with methylene chloride (3x20 mL), dried (MgSO4), and concentrated. The crude product was flash chromatographed using 3:1 hexanes:ethyl acetate as eluent to afford 670 mg (47%; 92% ee) of *S*-ester and 447 mg (37%; 98% ee) of *R*-alcohol (one overlap fraction). Enantiomeric excess was determined using a method analogous to that described in Dale et al, J. Org. Chem., 1969, Vol 33, p2543.

R-alcohol: $[\alpha]D^{20}$ +7.14° (c. 1.036, methanol)

S-ester: $[\alpha]D^{20}$ -5.29° (c. 1.324, methanol).

All properties of the alcohol and the ester are as reported above.

Reduction of the olefin of the *R*-alcohol afforded the corresponding (-)-1,2-butanediol monotosylate. This compound is known to possess the *R*-(-) configuration (Hamaguchi, et al, Agri. Biol. Chem. vol 50, pg 1629 (1986).

The following example is submitted for a further understanding of the invention:

Example 1

Selective Reaction of *R*-Alcohol with Potassium Bicarbonate in Ethylene Glycol

An approximately 1:1 mixture of enantiomerically enriched *R*-alcohol (92% ee) and *S*-ester (98% ee) (13.2 g; about 25 mmol each) formed as described above was dissolved in ethylene glycol (50 mL). Potassium bicarbonate (12.5 g; 125 mmol; 5 equiv. based on alcohol) was added, and the reaction mixture was sealed and stirred overnight (18 h) at room temperature to completely consume the alcohol. The EpB that was formed from the alcohol was distilled from the reaction mixture at about 5 mm Hg and collected in a -78°C trap to afford 489 mg (14% overall yield) of EpB (pure by ^{1}H nmr) which was 75% optically pure by optical rotation comparison. The residual reaction mixture was diluted with water (50 mL) and extracted with ether (3x50 mL). The combined extracts were dried (MgSO4) and concentrated to afford 5.85 g of enantiomerically enriched ester (41% from racemic ester).

The achiral properties are as previously reported. $[\alpha]D^{20}$ -16.1° (c. 0.998, pentane). Compared to previous values, this indicates 75% ee.

All properties of of the *S*-ester are as previously reported.

S-Hydroxy-tosylate

Enantiomerically enriched *S*-ester (5.85 g; 20.8 mmol) obtained above was dissolved in methanol (50 mL) and concentrated HCl (100 drops; 3.2 mL) was added. The resulting solution was stirred at room temperature for 24 hours to completely consume the ester as determined by thin layer chromotography analysis. The reaction mixture was diluted with ether (100 mL), washed with saturated sodium bicarbonate (3x20 mL), dried (MgSO4), and concentrated to afford 4.45 g (89%) of enantiomerically enriched alcohol(98% ee).

The *S*-alcohol was recrystallized from warm ether

(8 mL) by hexanes addition (12 mL) and chilling to -20°C to afford 3.74 g (75%; 31% yield from racemic esters) of *S*-alcohol, mp 62-64°C , substantially optically pure (>99% ee).

All achiral properties of the *S*-alcohol are as previously reported. $[\alpha]D^{20}$ -8.10° (c. 1.05, methanol).

Claims:

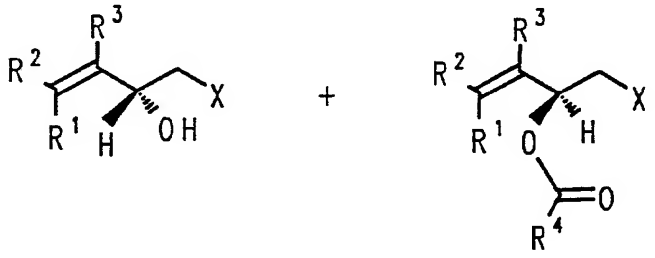
1. A process for the isolation of an enantiomerically enriched ester from a first mixture of an enantiomerically enriched alcohol and an enantiomerically enriched ester, said process comprising the steps of:

(a) contacting said mixture with a reagent capable of reacting with said alcohol to produce a second mixture containing enantiomerically enriched unreacted ester and a compound more volatile than said ester; said reagent comprising a metal bicarbonate and a polyhydroxy solvent containing from 2 to 4 carbon atoms; and

(b) removing the volatile compound from the second mixture, leaving behind enantiomerically enriched ester. The enantiomerically enriched ester can be used directly or can be converted to an enantiomerically enriched alcohol.

2. The process according to claim 1 wherein said bicarbonate is potassium bicarbonate and said polyhydroxy solvent is ethylene glycol.

3. The process according to claim 1 wherein said mixture is represented by the structures:



wherein each R is a group stable to mildly basic conditions and is independently selected from H, straight- or branched-chain substituted or unsubstituted alkyl, aryl, substituted aryl, arylalkyl, non-nitrogen-containing heteroaryl or substituted heteroaryl, or halogen;

X is selected from halogen or sulfonate esters.

4. The process according to claim 3 wherein said sulfonate esters are selected from the group consisting of p-toluenesulfonate, phenylsulfonate, p-bromobenzenesulfonate, 4-chloro-3-nitrobenzenesulfonate, 2,5-dichlorobenzenesulfonate, 5-dimethylamino-1-naphthalenesulfonate, 2,4-dinitrobenzenesulfonate, p-iodobenzenesulfonate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, o-nitrobenzenesulfonate, m-nitrobenzenesulfonate, p-nitrobenzenesulfonate, 2-thiophenesulfonate, methanesulfonate and trifluoromethanesulfonate.

5. A process according to claim 1 wherein said first mixture is produced by the enzymatic enantioselective hydrolysis of a racemic ester.

6. The process according to claim 5 wherein said racemic ester is derived from epoxybutadiene.

7. A process according to claim 1 wherein said first mixture is a mixture of 1-tosyloxy-2-hydroxy-3-butene and 1-tosyloxy-2-acetoxy-3-butene.

8. A process according to claim 1 wherein said volatile compound formed in step (a) is epoxybutadiene.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/02111

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 C 309/73, C 07 C 303/44

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 C 309/00, C 07 C 303/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
	No relevant documents have been disclosed	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th June 1991	09. 09. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

Form PCT/ISA/210 (second sheet) (January 1985)